IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Turner, Jr. and Mathur		
Serial No.:	09/714,883	Group Art Unit:	1646
Filed:	11/16/2000	Examiner:	O. Chernyshev
For:	Novel Human Secreted Proteins and Polynucleotides Encoding the Same	Attorney Docket No.:	LEX-0092-USA

#16
D.J
9/27/02

AMENDED APPEAL BRIEF

Box AF
Assistant Commissioner for Patents
Washington, D.C. 20231

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AMENDED APPEAL BRIEF

Sir:

Appellants hereby submit an original and two copies of this Amended Appeal Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Final Office Action mailed on February 19, 2002, replacing the Appeal Brief filed by Appellants on September 23, 2002, which was not filed in triplicate. The Notice of Appeal was timely submitted on May 17, 2002, and was received in the Patent and Trademark Office ("the Office") on May 21, 2002. This Appeal Brief is timely submitted in light of the concurrently filed Petition for an Extension of Time of three months to and including October 21, 2002, and authorization to deduct the additional fee as required under 37 C.F.R. § 1.17(a)(3) from Lexicon Genetics Incorporated Deposit Account No. 50-0892. The Commissioner was previously authorized (in the original Appeal Brief filed September 23, 2002) to charge the fee for filing an Appeal Brief ($160.00), as required under 37 C.F.R. § 1.17(c), and the fee for a two month extension of time as required under 37 C.F.R. § 1.17(a)(3) to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

Appellants believe no fees in addition to the additional one month extension of time (in addition to the fee for filing the original Appeal Brief and the two month extension, which were authorized in the original Appeal Brief filed September 23, 2002) are due in connection with this Amended Appeal Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee, Lexicon Genetics Incorporated, 8800 Technology Forest Place, The Woodlands, Texas, 77381.

II. RELATED APPEALS AND INTERFERENCES

Appellants know of no related appeals or interferences.

III. STATUS OF THE CLAIMS

The present application was filed on November 16, 2000, and included original claims 1-3. A First Official Action on the merits ("the First Action") was issued on July 9, 2001, in which claims 1-3 were rejected under 35 U.S.C. § 101 as allegedly lacking a patentable utility, claims 1-3 were rejected under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, and claim 2 was rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. In a response to the First Official Action submitted to the Office on November 8, 2001, Appellants amended claim 2 to further improve its clarity.

A Second and Final Official Action ("the Final Action") was mailed on February 9, 2002, indicating that the rejection of claim 2 under 35 U.S.C. § 112, second paragraph had been overcome by the amendment submitted in Appellants response, but maintaining the rejection of claims 1-3 under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility. In a response to the Second and Final Office Action submitted on April 17, 2002, Appellants did not amend the pending claims, and did not add any new claims. Therefore, claims 1-3 are the subject of this appeal. A copy of the appealed claims are included below in the Appendix (Section IX).

IV. STATUS OF THE AMENDMENTS

As no amendments have been filed subsequent to the final rejection, Appellants believe that no outstanding amendments exist.

V. SUMMARY OF THE INVENTION

The present invention relates to Appellants' discovery and identification of novel human polynucleotide sequences that encode proteins sharing sequence similarity with mammalian ceruloplasmins. Ceruloplasmins are members of a family of metal chelating proteins that have been associated with, among other functions, copper transport (specification at page 1, lines 23-25). The copper transport function of ceruloplasmins have been associated with Wilson's disease, and as such, ceruloplasmins have a role in the

treatment of Wilson's disease (specification at page 12, lines 1-2).

The presently claimed polynucleotide sequences were obtained from human gene trapped sequence tags and cDNA clones from a human mammary gland cDNA library (specification at page 13, lines 4-6). A coding region single nucleotide polymorphism, consisting of a G-to-A transition at position 1756 of SEQ ID NO:1, which can result in the presence of a valine or an isoleucine residue at the corresponding amino acid position 586 of SEQ ID NO:2, was identified in the claimed polynucleotide sequence (specification at page 13, lines 6-11).

In addition to the use in the treatment of Wilson's disease, as described above, the presently claimed polynucleotide sequences have a number of other uses, including assessing gene expression patterns, particularly using a high throughput "chip" format (specification at page 5, lines 6-8), determining the genomic structure (specification at page 7, line 32), and designing diagnostic tests based on the single nucleotide polymorphism described in SEQ ID NO:1 (specification from page 7, line 29 through page 8, line 6).

VI. ISSUES ON APPEAL

1. Do Claims 1-3 lack a patentable utility?
2. Are Claims 1-3 unusable by a skilled artisan due to a lack of patentable utility?

VII. GROUPING OF THE CLAIMS

For the purposes of all outstanding rejections, the claims will stand or fall together.

VIII. ARGUMENT

A. Do Claims 1-3 Lack a Patentable Utility?

The Final Action first rejects claims 1-3 under 35 U.S.C. § 101, as allegedly lacking a patentable utility due to not being supported by either a specific and substantial utility or a well-established utility.

In the First Action, the Examiner seemed to be requiring data "which associates the instant DNA or encoded protein with any diseases or disorder" or that shows the "use of the protein as a marker for any

disease or condition" (the First Action at page 4). This is reiterated in the Final Action, with the Examiner stating that the "instant claims are drawn to a DNA and the protein encoded thereby of as yet undetermined function or biological significance" (the Final Action at page 2). However, this position as applied to the presently claimed sequences is wholly unsupported by mandatory legal precedent. First, it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 309 F.2d 769, 135 USPQ 311 (CCPA, 1962).

Furthermore, Appellants would like to invite the Board's attention to the fact that sequences sharing 57% percent identity at the protein level with the described sequence are present in the leading scientific repository for biological sequence data (GenBank), and have been annotated by third party scientists *wholly unaffiliated with Appellants* as "human ceruloplasmin" (GenBank accession number M13699; **Exhibit A**) and "homo sapiens ceruloplasmin" (GenBank accession number NM_000096; **Exhibit B**). The legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable. Given these GenBank annotations, there can be no question that those skilled in the art would clearly believe that Appellants' sequence is a ceruloplasmin. Furthermore, the Examiner admits that the claimed sequence is a "member of the ceruloplasmin family of metal chelating proteins" (the Final Action at page 3).

With regard to the Examiner's statement in the First Action that there is no data "which associates the instant DNA or encoded protein with any diseases or disorder" or that shows the "use of the protein as a marker for any disease or condition" (the First Action at page 4), Appellants point out for the record that the association between ceruloplasmin and Wilson's disease was discussed in the present application, at least at page 12, lines 1-2, and, further, that this relationship between ceruloplasmin and Wilson's disease has long been recognized by skilled artisans. This is evidenced by a steady stream of scientific manuscripts describing the relationship between Wilson's disease and ceruloplasmin, with the first such manuscripts published as early as 1965, and the description of this relationship in hundreds of scientific manuscripts. This is evidenced by the index of PubMed citations containing the terms Wilson's disease and ceruloplasmin, which is shown in **Exhibit C**. Thus, ceruloplasmins, such as the presently described protein, have a well-established utility, as the relationship between Wilson's disease and ceruloplasmin is very well-

known in the art. Additionally, it is known that different ceruloplasmin isoforms serve as an accurate marker for Wilson's disease (for example, see Chowrimootoo *et al.*, 1998, Arch. Dis. Child Fetal Neonatal Ed. 79:F198-201; **Exhibit D**). Thus, the skilled artisan would readily appreciate the utility associated with the provision of novel human sequences related to ceruloplasmin, and therefore, the present utility rejection must fail. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

The Examiner states that "(t)he protein of the instant invention does not belong to a family of compounds with a common, well established specific and substantial utility" (the Final Action at page 3). However, the evidence provided herewith conclusively establishes that this is clearly not the case. Thus, Appellants reliance on *In re Brana,* (34 USPQ2d 1436 (Fed. Cir. 1995), "*Brana*") in the response to the First Action is not at all "misplaced" (the Final Action at page 3). In *Brana*, the Federal Circuit admonished the P.T.O. for confusing "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption". *Brana* at 1442. The Federal Circuit went on to state:

> At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant provide regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago.

Brana at 1439, emphasis added. The choice of the phrase "utility or usefulness" in the foregoing quotation is highly pertinent. The Federal Circuit is evidently using "utility" to refer to rejections under 35 U.S.C. § 101, and is using "usefulness" to refer to rejections under 35 U.S.C. § 112, first paragraph. This is made evident in the continuing text in *Brana*, which explains the correlation between 35 U.S.C. §§ 101 and 112, first paragraph. The Federal Circuit concluded:

> FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before

> it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

Brana at 1442-1443, citations omitted, emphasis added. In assessing the question of whether undue experimentation would be required in order to practice the claimed invention, the key term is "undue", not "experimentation". *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). The need for some experimentation does not render the claimed invention unpatentable. Indeed, a considerable amount of experimentation may be permissible if such experimentation is routinely practiced in the art. *In re Angstadt and Griffin, supra*; *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). As a matter of law, it is well settled that a patent need not disclose what is well known in the art. *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir. 1988).

Rather, regarding the utility requirements under 35 U.S.C. § 101, the Federal Circuit has clearly stated "(t)he threshold of utility is not high: An invention is 'useful' under section 101 if it is capable of providing some identifiable benefit." *Juicy Whip Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 51 USPQ2d 1700 (Fed. Cir. 1999) (citing *Brenner v. Manson*, 383 U.S. 519, 534 (1966)). Additionally, the Federal Circuit has stated that "(t)o violate § 101 the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571, 24 USPQ2d 1401 (Fed. Cir. 1992), emphasis added. *Cross v. Iizuka* (753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); "*Cross*") states "any utility of the claimed compounds is sufficient to satisfy 35 U.S.C. § 101". *Cross* at 748, emphasis added. Indeed, the Federal Circuit recently emphatically confirmed that "anything under the sun that is made by man" is patentable *(State Street Bank & Trust Co. v. Signature Financial Group Inc.*, 149 F.3d 1368, 47 USPQ2d 1596, 1600 (Fed. Cir. 1998), citing the U.S. Supreme Court's decision in *Diamond vs. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (U.S., 1980)).

As discussed in the response to the First Action, the specification teaches that the present nucleotide sequence encodes a human ceruloplasmin, and that ceruloplasmins are associated with many human diseases, including Wilson's disease. Furthermore, the described sequence provides a specific marker of the human genome, and that such specific markers are targets for discovering drugs that are

associated with human disease. Thus, those skilled in the art would instantly recognize that the present nucleotide sequence would be an ideal, novel candidate for assessing gene expression using, for example, DNA chips, as the specification details at least on page 5, lines 5-8. Such "DNA chips" clearly have utility, as evidenced by hundreds of issued U.S. Patents, as exemplified by U.S. Patent Nos. 5,445,934 (**Exhibit** E), 5,556,752 (**Exhibit** F), 5,744,305 (**Exhibit** G), and others listed on page 50 of the specification as filed, as well as more recently issued U.S. Patent Nos. 5,837,832 (**Exhibit** H), 6,156,501 (**Exhibit** I) and 6,261,776 (**Exhibit** J). Given the widespread utility of such "gene chip" methods using *public domain* gene sequence information, there can be little doubt that the use of the presently described *novel* sequences would have great utility in such DNA chip applications. Accordingly, as opposed to the contention in the Action that "any nucleic acid encoding a protein, which is differentially expressed, can be employed in a DNA chip for assessing gene expression patterns" (the Final Action at page 3), the present sequence, with its well-established medical relevance, has a specific utility in such DNA chip applications. Clearly, compositions that enhance the utility of such DNA chips, such as the presently claimed nucleotide sequence, must also be useful. Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Evidence of the "real world" substantial utility of the present invention is further provided by the fact that there is an entire industry established based on the use of gene sequences or fragments thereof in a gene chip format. Perhaps the most notable gene chip company is Affymetrix. However, there are many companies which have, at one time or another, concentrated on the use of gene sequences or fragments, in gene chip and non-gene chip formats, for example: Gene Logic, ABI-Perkin-Elmer, HySeq and Incyte. In addition, two such companies (Agilent acquired by American Home Products and Rosetta acquired by Merck) were viewed to have such "real world" value that they were acquired by large pharmaceutical companies for significant sums of money. The "real world" substantial industrial utility of gene sequences or fragments would, therefore, appear to be widespread and well established. Clearly, persons of skill in the art, as well as venture capitalists and investors, readily recognize the utility, both scientific and commercial, of genomic data in general, and specifically human genomic data. Billions of dollars have been invested in the human genome project, resulting in useful genomic data (see, *e.g.*, Venter *et al.*, 2001, Science *291*:1304; **Exhibit** K). The results have been a stunning success as the utility of human genomic

data has been widely recognized as a great gift to humanity (see, *e.g.*, Jasny and Kennedy, 2001, Science *291*:1153; **Exhibit** L). Clearly, the usefulness of human genomic data, such as the presently claimed nucleic acid molecules, is substantial and credible (worthy of billions of dollars and the creation of numerous companies focused on such information) and well-established (the utility of human genomic information has been clearly understood for many years).

As yet another example of utility of the present nucleotide sequence, the present nucleotide sequence has a specific utility in determining the genomic structure of the corresponding human chromosome, for example mapping the protein encoding regions, as described in the specification at least at page 7, line 32. Clearly, the present polynucleotide provides exquisite specificity in localizing the specific region of the human chromosome containing the gene encoding the given polynucleotide, a utility not shared by virtually any other nucleic acid sequences. In fact, it is this specificity that makes this particular sequence so useful. Early gene mapping techniques relied on methods such as Giemsa staining to identify regions of chromosomes. However, such techniques produced genetic maps with a resolution of only 5 to 10 megabases, far too low to be of much help in identifying specific genes involved in disease. The skilled artisan readily appreciates the significant benefit afforded by markers that map a specific locus of the human genome, such as the present nucleic acid sequence. This is even more true when the genetic locus has been unambiguously linked to human disease (in this particular instance, Wilson's disease).

Although Appellants need only make one credible assertion of utility to meet the requirements of 35 U.S.C. § 101 (*Raytheon v. Roper*, 220 USPQ 592 (Fed. Cir. 1983); *In re Gottlieb*, 140 USPQ 665 (CCPA 1964); *In re Malachowski*, 189 USPQ 432 (CCPA 1976); *Hoffman v. Klaus*, 9 USPQ2d 1657 (Bd. Pat. App. & Inter. 1988)), as a further example of the utility of the presently claimed polynucleotide, as described in the specification, at least from page 7, line 29 through page 8, line 6, the present polynucleotide sequence has utility in designing diagnostic tests based on the single nucleotide polymorphism described in SEQ ID NO:1 As described in the specification at specification at page 13, lines 6-11, a coding region single nucleotide polymorphism, consisting of a G-to-A transition at position 1756 of SEQ ID NO:1, which can result in the presence of a valine or an isoleucine residue at the corresponding amino acid position 586 of SEQ ID NO:2, was identified in the claimed polynucleotide

sequence. As such polymorphisms are the basis for forensic analysis, which in undoubtedly a "real world" utility, the present sequences must in themselves be useful. It is important to note that the presence of more useful polymorphic markers for forensic analysis would not mean that the present sequences lack utility.

Furthermore, the Examiner is respectfully reminded that only a minor percentage of the genome actually encodes exons, which in-turn encode amino acid sequences. The presently claimed polynucleotide sequence provides biologically validated empirical data (*e.g.*, showing which sequences are transcribed, spliced, and polyadenylated) that *specifically* define that portion of the corresponding genomic locus that actually encodes exon sequence. Equally significant is that the claimed polynucleotide sequence defines how the encoded exons are actually spliced together to produce an active transcript (*i.e.*, the described sequences are useful for functionally defining exon splice-junctions). The Appellants respectfully submit that the practical scientific value of expressed, spliced, and polyadenylated mRNA sequences is readily apparent to those skilled in the relevant biological and biochemical arts. For further evidence in support of the Appellants' position, the Examiner is requested to review, for example, section 3 of Venter *et al.* (*supra at* pp. 1317-1321, including Fig. 11 at pp.1324-1325), which demonstrates the significance of expressed sequence information in the structural analysis of genomic data. The presently claimed polynucleotide sequence defines a biologically validated sequence that provides a unique and specific resource for mapping the genome essentially as described in the Venter *et al.* article Thus, the present claims clearly meet the requirements of 35 U.S.C. § 101.

Finally, the requirements set forth in the Action for compliance with 35 U.S.C. § 101 do not comply with the requirements set forth by the Patent and Trademark Office ("the PTO") itself for compliance with 35 U.S.C. § 101. The PTO has issued numerous patents on polynucleotide sequences that have not been directly shown to be associated "with any diseases or disorder" or useful as "a marker for any disease or condition", the conditions set forth by the Examiner as allegedly necessary to comply with 35 U.S.C. § 101. As examples of such issued U.S. Patents, the Examiner is invited to review U.S. Patent Nos. 5,817,479 (**Exhibit M**, 5,654,173 (**Exhibit N**), and 5,552,281 (**Exhibit O**; each of which claims short polynucleotides), and recently issued U.S. Patent No. 6,340,583 (**Exhibit P**; which includes no working examples), none of which contain examples of the "real-world" utilities that the Examiner seems

to be requiring in the present Action. As issued U.S. Patents are presumed to meet all of the requirements for patentability, including 35 U.S.C. §§ 101 and 112, first paragraph (see Section VIII(B) below), Appellants submit that the presently claimed polynucleotides must also meet the requirements of 35 U.S.C. § 101.

For each of the foregoing reasons, Appellants submit that the rejection of claims 1-3 under 35 U.S.C. § 101 must be overruled.

B. Are Claims 1-3 Unusable Due to a Lack of Patentable Utility?

The Final Action next rejects claims 1-3 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility.

The arguments detailed above in Section VIII(A) concerning the utility of the presently claimed sequences are incorporated herein by reference. As the Federal Circuit and its predecessor have determined that the utility requirement of Section 101 and the how to use requirement of Section 112, first paragraph, have the same basis, specifically the disclosure of a credible utility (*In re Brana, supra*; *In re Jolles*, 628 F.2d 1322, 1326 n.11, 206 USPQ 885, 889 n.11 (CCPA 1980); *In re Fouche*, 439 F.2d 1237, 1243, 169 USPQ 429, 434 (CCPA 1971)), Appellants submit that as claims 1-3 have been shown to have "a specific, substantial, and credible utility", as detailed in Section VIII(A) above, the present rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-3 under 35 U.S.C. § 112, first paragraph, must be overruled.

IX. APPENDIX

The claims involved in this appeal are as follows:

1. An isolated nucleic acid molecule comprising at least 24 contiguous bases of nucleotide sequence first disclosed in the NHP polynucleotide described in SEQ ID NO:1.

2. (Amended) An isolated nucleic acid molecule comprising a nucleotide sequence that:

(a) encodes the amino acid sequence shown in SEQ ID NO:2; and

(b) hybridizes under highly stringent conditions to the nucleotide sequence of SEQ ID NO: 1 or the complement thereof.

3. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the amino acid sequence shown in SEQ ID NO:2.

X. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-3 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

September 24, 2002
Date

David W. Hibler
Agent For Appellants

Reg. No. 41,071

LEXICON GENETICS INCORPORATED
(281) 863-3399

TABLE OF AUTHORITIES

CASES

STATUTES